REMARKS/ARGUMENTS

Application Amendments

By the amendments presented, Claim 1 is rewritten to characterize the bacteria being detected as being "wound-specific". Support for this amendment to Claim 1 is found in originally filed Claim 2. Claims 2 is accordingly rewritten editorially to take into account the incorporation of subject matter therefrom into Claim 1 from which Claim 2 depends.

Also by the amendments presented, Claim 1 is rewritten to characterize via a Markush group the peptide substrate which is employed in the claimed method as comprising one of the five amino acid sequences listed in Claim 5 as originally filed. Claim 1 is further amended to characterize the peptide substrate used as also possibly comprising "a variant, homolog or fragment" of any of the five amino acid sequences recited. Support for addition of this phrase to Claim 1 can be found in the originally filed specification at Page 4, lines 1-2 and Page 14, lines 13 to 25. An extensive discussion of what constitutes variants, homologs and fragments of the serpin peptide substrates is also found in the original specification from Page 14, line 26 to Page 16, line 31.

Also by the amendments presented, Claim 1 is further rewritten to characterize the enzyme which cleaves the substrate as being a "protease". Support for this Claim 1 amendment is found in original Claim 3 which is accordingly cancelled herein.

Also by the amendments presented, Claim 5 is rewritten to recite only the preferred CPI2 peptide substrate (SEQ ID No. 2) and its variants, homologs and fragments. The other peptide substrate amino acid sequences recited in original Claim 5 are cancelled from Claim 5 since they have now been recited in amended Claim 1 instead.

Upon entry of the claim amendments presented, Claims 1, 2 and 4-12 remain in the application. No additional claims fee is due as a result of these claim amendments.

Invention Synopsis

By way of review, the present invention as now claimed is directed to a method for detecting the presence or absence of a wound-specific bacterium in a sample which can be a wound surface or a body fluid or other fluid taken from a wound. Detection of the presence or

absence of the wound-specific bacterium makes it possible to detect or diagnose infection of the wound with a broad spectrum of pathogenic microorganisms.

In the first step of this method, the sample is contacted with a surface-attached, detectably labeled synthetic α1-proteinase inhibitor reactive site loop domain peptide substrate under conditions that result in cleavage of the substrate by a protease enzyme produced in the sample by a wound-specific bacterium. The peptide substrate used comprises one of five amino acid sequence listings or variants, homologs or fragments thereof. In the second step of the method, cleavage or an absence of the cleavage of the substrate is detected with the cleavage of the substrate indicating the presence of the bacterium in the sample and absence of the cleavage of the substrate indicating absence of the bacterium in the sample.

In preferred invention embodiments, detection of cleavage or no cleavage of the peptide substrate is effected by labeling the substrate with a label such as a spin label, antigen tag, epitope tag, hapten, enzyme label, prosthetic group, fluorescent material, pH-sensitive material, chemiluminescent material, colorimetric component, bioluminescent material, and/or radioactive material. The surface to which the peptide substrate is attached or anchored is also preferably a polymer, membrane, resin, glass or sponge and is associated with a solid support such as a wound dressing, a container for holding body fluids, a disk, a scope, a filter, a lens, a foam, a cloth, a paper, a suture, a dipstick, a swab, a urine collection bag, a blood collection bag, a plasma collection bag, a test tube, a catheter, and/or a well of a microplate.

Claim Rejection

In the instant November 6, 2009 Office Action, the Examiner has maintained the previous rejection of Claims 1-12 under 35 U.S.C. §112, First Paragraph, as allegedly being insufficiently supported by the written description with respect to the detection of the presence or absence of bacteria in the wound sample by means of detecting the presence or absence of enzymes released by the bacteria. The Examiner continues to contend, citing several publications, that enzymes, such as host matrix metalloproteinases (MMPs) which also cleave the specified peptide substrates, are released from neutrophils and macrophages during wound infection/healing. The Examiner thus urges that such metalloproteinases would also be detected by the claimed method, thereby "confounding" use of the method to detect presence or absence of pathogenic wound-infecting bacteria. The Examiner further urges that the specification

examples illustrating the method of Claims 1-12 fail to provide enough information about the wounds being investigated and nature of the bacteria therein to teach the skilled artisan how to practice the bacterium detection method of rejected Claims 1-12. Such a rejection is respectfully traversed as it would apply to the amended claims presented herein.

In response to the Examiner's position concerning the Section 112 rejection of the application claims, applicants submitted a Declaration Under 37 CFR §1.132 of Mitchell C. Sanders, one of the inventors named in the present application. In connection with this Rule 132 Declaration, applicants also submitted copies of a paper for proposed publication entitled "Rapid Measurement of Protease Activity Prevalent in Bacteria from Wounds: A Diagnostic for Total Bioburden" and a poster entitled "Integration of a Diagnostic Into an Advanced Wound Care Dressing".

It is applicants' position that the information provided in the Sanders Rule 132 Declaration and in the accompanying proposed publication and poster demonstrates that the bacterium detection method of the claims as amended herein is highly effective at detecting pathogenic bacteria present in wounds or wound fluids. Applicants further continue to maintain that this Rule 132 Declaration demonstrates that the peptide substrates used are not significantly cleaved by any host enzymes such as MMPs which might be present in wounds instead of pathogenic bacteria. In short, applicants submit that the Rule 132 Declaration of record demonstrates the invalidity of the Examiner's speculative theory that the method of the applicants' claims would be "confounded" by the detection of enzymes present from other than pathogenic bacteria. Rather, the Rule 132 Declaration and the extensive clinical study documented in the accompanying proposed publication provides further evidence of the effectiveness of using bacteria-produced protease as a marker for early detection of wound infection by pathogenic microorganisms.

In the instant Office Action, the Examiner takes the position that the Sanders Rule 132 Declaration is insufficient to overcome the Section 112 rejection because its "objective evidence of nonobviousness" is not commensurate in scope with the claims. The Examiner is reminded that "nonobviousness" or the lack thereof is not an element or issue in determining the propriety of a rejection under Section 112, First Paragraph. Nevertheless, it is assumed that the Examiner meant to contend that while the Sanders Rule 132 Declaration shows that there are some narrow method embodiments within applicants' claims which are operable, there would be other

embodiments within the claims which would still be "confounded" by the presence in test samples of host proteases.

In taking this position, the Examiner asserts, for example, that the Rule 132 Declaration shows operability only of methods using alpha-1-trypsin peptide substrates anchored to a certain type of beads and a certain type of aromatic markers. All three of these elements, however, are appropriately representative of the types of materials which can be used in the claimed method. The Examiner has provided no reasoning or evidence as to why alternatives to these elements encompassed by the presently amended claims would not also be operable.

The Examiner further takes the position that the Rule 132 Declaration demonstrates that the claimed method is especially effective when a CPI2S substrate is used but that CPI2S is allegedly not disclosed or claimed. It is respectfully submitted that such allegations are not correct. The Rule 132 Declaration clearly shows that both the the CPI2 and CPI2S substrates are operable in the bacteria detection method even though the CPI2S substrate is even more selective to being clipped by bacterial proteases than is the CPI2 substrate. The CPI2S substrate, however, is quite obviously just a fragment of the CPI2 substrate. And such fragments are clearly and extensively described, a nd now expressly claimed, in the application as being suitable and workable alternatives to the specific substrates which have their longer amino acid sequences set forth.

It is also submitted that the Examiner's contention that MMPs cross react with the claimed substrates is contrary to *in vivo* and *in vitro* data provided in the Sanders Rule 132 Declaration. *In vivo* clinical data from the referenced proposed publication demonstrate a very strong overall accuracy for correlating to bio burden (total bacterial load) in chronic wounds. The *in vitro* data provided demonstrate that the anchored substrates used do not cross react with MMPs 1, 2, 9, 12, and 13. Furthermore, even though human neutrophil elastase (HNE) can react with peptides such as CPI2, there is clinical evidence to suggest that HNE is normally only active when there is a high bacterial load to activate the pro-enzyme.

It is not disputed that host proteases can be found in wounds. However, it is applicants' position that the presence of such host proteases, including MMPs and HNE, is irrelevant in the context of applicants' diagnostic development. In short, it is submitted that such host proteases do not materially interfere with the sensitivity or specificity of the diagnostic assay method for detecting the presence or absence of wound-specific bacteria as now claimed.

Given the foregoing considerations, it is again submitted that the specification of the present application teaches the skilled artisan in sufficient detail how to prepare the surface-attached, detectably labeled specific peptide substrates of the present invention and how to use such substrates in the claimed bacterium detection method. Accordingly, it can be seen that the bacterium detection method of the present invention is fully supported by the written description of the specification and is fully operable as claimed. Continued rejection of the amended claims under 35 U.S.C. §112, First Paragraph, would therefore be improper.

Conclusions

Applicants have made an earnest effort to place their application in proper form, to demonstrate the operability of their invention, and to claim their invention in a manner which is fully supported by the enabling disclosure of the specification. WHEREFORE, reconsideration of this application, entry of the claim amendments presented herein, reconsideration of the previously submitted Declaration of Mitchell C. Sanders Under 37 CFR §1.132 and accompanying documentation submitted herewith, withdrawal of the claim rejection under 35 U.S.C. §112, First Paragraph, and allowance of Claims 1, 2 and 4-12 as amended, are all respectfully requested.

Any comments or questions concerning this application can be directed to the undersigned at the telephone number given below.

Respectfully submitted,

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By: _____

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